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Title: Pathogenesis of Lethal Cardiac Arrhythmias in Mecp2 Mutant Mice: Implication for Therapy in Rett Syndrome

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Although many people with Rett syndrome live long lives, up to a quarter of all deaths in Rett syndrome are sudden and unexpected. Dr. Neul and his colleagues explored the hypothesis that these deaths are due to cardiac dysfunction. Using data collected in the Rett Syndrome Natural History Study, they found that nearly 20% of those with Rett syndrome exhibit changes in the way their hearts conduct electricity. This type of problem can make the heart suddenly start beating very fast (tachycardia), which can lead to an inefficient distribution of blood and result in sudden death.

The authors have sought to identify the underlying cause of this cardiac dysfunction in the mouse models of RTT. They have found that RTT mice also have this same electrical problem in their hearts, and can develop this fast heart beat and die. The specific dysfunction is a prolonged QT interval (LQT), which is a measure of the time between two electrical waves in the heart's electrical cycle. Interestingly, the authors report that these cardiac abnormalities are more apparent in older mice, suggesting that the development of this dysfunction occurs in an age-dependent fashion and is likely a secondary effect to the loss of MeCP2 in the nervous system.

The current standard of care for LQT in RTT patients is a  $\beta$ -adrenergic receptor blocker; however, the authors reported that this drug did not prevent the rapid heart rate in the RTT mouse model. They found that sodium channels were persistently turned on in isolated heart cells, and therefore focused on drugs which function to block the sodium channels. By giving these animals a single dose of the anti-epileptic drug Phenytoin (PHT), a sodium channel blocker, they were able to change the electrical activity and prevent the RTT mice from having the fast heart rate. Therefore, PHT can shorten the LQT electrical problem, reduce rapid heart rate, and prevent sudden cardiac death, raising the possibility that such treatments may prove effective in people with RTT.

Additional information will be gained as the Rett Syndrome Natural History Study progresses and more information can be gathered with repeated cardiac function measurements in RTT patients. It would also be beneficial to determine from the human data whether exposure to specific drugs or specific *MECP2* mutations alter the susceptibility towards developing LQT and rapid heart rate. As mentioned above, at present, PHT or other sodium channel blocking agents are not the standard of care for LQT in RTT. These drugs are commonly used in neurological diseases for their anti-seizure effects, but could also be useful for preventing cardiac arrhythmias. Future work will identify the best therapeutic option Rett syndrome.

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